Exercise Intolerance

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OBJECTIVES

After completing this article, the reader should be able to:

1. **Explain the causes of exercise intolerance.**
2. **List the two most useful diagnostic tools for assessing exercise intolerance.**
3. **Describe how pulmonary dysfunctions, cardiac diseases, and muscular disorders affect exercise tolerance.**
4. **Delineate the nonpharmacologic treatment of choice for most cases of exercise intolerance.**
5. **Explain the role of behavioral modification within a family-based intervention for exercise intolerance.**

Introduction

Exercise intolerance is a general term associated with individuals whose responses to the challenges of exercise fail to achieve levels considered normal for their age and gender. In the pediatric population, exercise intolerance most frequently is associated with dysfunctions of the pulmonary, cardiovascular, and neuromuscular systems, although psychogenic and behavioral causes also place large numbers of children at risk. The reference standard for determining exercise intolerance is the maximal oxygen consumption ($\dot{V}O_2$ max) test. Identifying perturbations in components of the Fick equation (Figure) associated with this test is useful for diagnosis, for explaining signs and symptoms, and for evaluating therapeutic interventions. In this brief review we examine some commonly encountered pediatric disorders associated with exercise intolerance.

Pulmonary Disorders

The two most common childhood pulmonary disorders associated with exercise intolerance are exercise-induced asthma (EIA) and cystic fibrosis (CF). Exercise intolerance may be a presenting symptom for other chronic lung dysfunctions, such as interstitial lung disease and alveolar proteinosis, but these are less common and are not discussed here.

EXERCISE-INDUCED ASTHMA (EIA)

Bronchoconstriction that develops during, or especially after, exercise is termed EIA. The prevalence of EIA in young people who have asthma ranges between 60% and 95%, depending on the exercise stimulus. In addition, EIA is seen in approximately 10% of children who have no apparent history of asthma. The pathogenesis of EIA is thought to be associated with the fluxes in heat and water that develop within the tracheobronchial tree with the high ventilation levels elicited by exercise. The cooling and drying of the respiratory mucosa results in osmolarity changes that can cause mast cell degranulation and the release of chemical mediators that trigger bronchoconstriction. Also, postexercise airway rewarming may induce hyperemia and edema, further compromising airway diameter. This series of events impinges on the oxygen content of arterial blood (CaO_2) component of the Fick equation (Figure) and results in exercise intolerance by reducing the CaO_2 through a subnormal arterial oxygen pressure and mild oxygen desaturation.

In a child known to have asthma, EIA usually can be diagnosed on the basis of history alone, that is, repeated complaints of dyspnea, chest tightness, cough, or wheezing after exercise. The diagnosis can be confirmed by a 15% or greater decrement in peak expiratory flow rate or forced expiratory volume in 1 second (FEV_1) 5 to 10 minutes following an exercise test.

The treatment of choice for EIA is a $beta_2$ agonist bronchodilator such as albuterol, which appears to be effective for more than 90% of patients when administered 10 to 15 minutes prior to exercise. The pressurized metered-dose inhaler is the preferred mode of delivery because of its convenience, lower dosage requirements, and better side effects profile. An alternative drug, cromolyn sodium, completely prevents EIA in approximately 50% of patients and may be used in combination with a $beta_2$ agonist when either agent by itself does not provide adequate therapy. Nonpharmacologic strategies include prolonged warmup and cool-down periods before and after exercise sessions, aerobic training programs, and avoidance of cold, dry exercise environments.

CYSTIC FIBROSIS (CF)

CF is the most commonly inherited genetic disease in Caucasians, affecting approximately 1 in 2,000 live births in this population, but it is rare among Americans of African and Asian descent. CF is characterized by excessive production of abnormal mucus secretions, which accumulate along the respiratory tract, leading to airway obstruction, chronic cough, and difficulty breathing. The degree of exercise intoler-

ABBREVIATIONS

CaO_2:	oxygen content of arterial blood
CF:	cystic fibrosis
EIA:	exercise-induced asthma
FEV_1:	forced expiratory volume in 1 second
Hb:	hemoglobin
$\dot{V}O_2$ max:	maximal oxygen consumption
SCA:	sickle cell anemia

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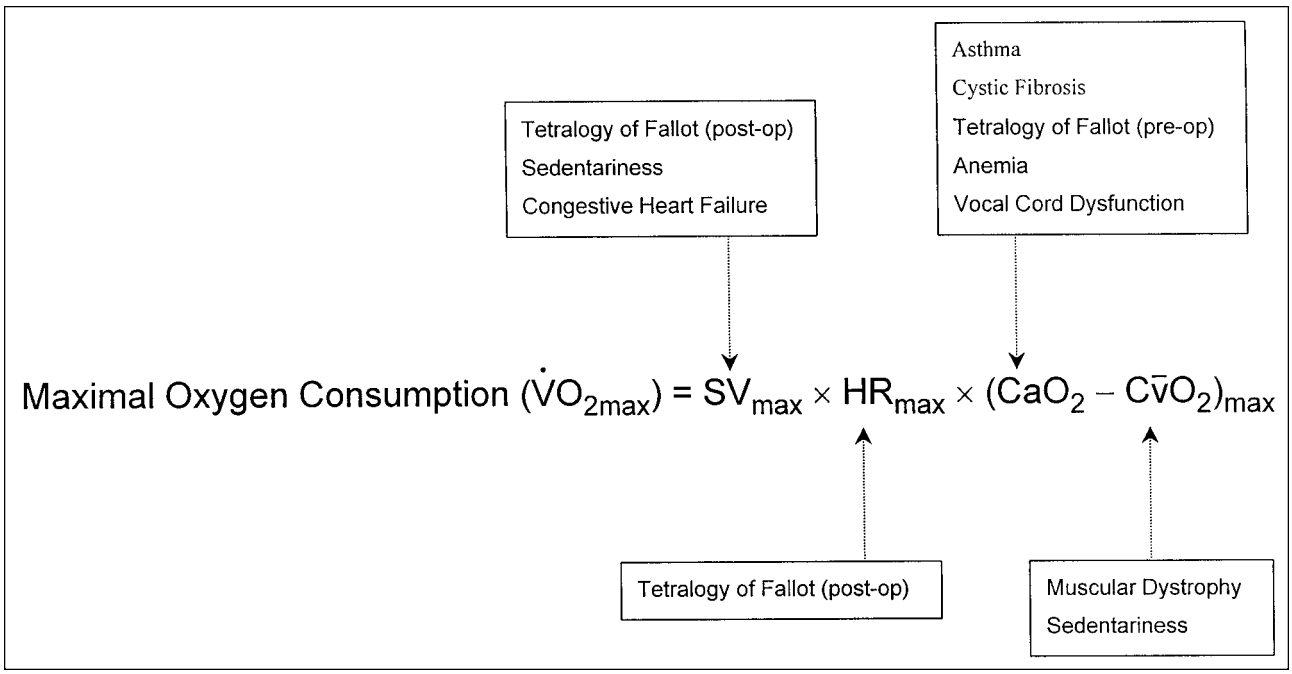

FIGURE. Fick equation for maximal oxygen consumption ($\dot{V}O_2$ max) and associated pediatric conditions that adversely affect its components. SV = stroke volume, HR = heart rate, CaO_2 = oxygen content of arterial blood, CvO_2 = oxygen content of mixed venous blood.

ance in CF appears to be related to the extent of lung disease and compromised nutritional status. To compensate for increased airway obstruction and dead space, those who have CF often employ a large minute ventilation during exercise, which both compromises ventilatory reserve and diverts cardiac output away from other exercising muscles. Also, there may be a ventilation/perfusion mismatch in moderate-to-severe lung disease, resulting in perturbations to the Fick equation in terms of oxygen desaturation and CO_2 retention.

An incremental exercise test can be used to determine the degree of exercise intolerance in CF. Pulmonary function tests such as $FEV_{1,}$ which are useful tools in the management of CF, appear to be of limited use in evaluating exercise intolerance for individual patients.

Exercise training can be an important component of care for those who have CF. In general, physical training studies have reported improvements in exercise tolerance and ventilatory muscle performance. Less consistent results have been reported for pulmonary function. Because the optimal dose of exercise training has yet to be identified, guidelines for normal children that are scaled down to the levels attainable by CF patients probably are appropriate.

Cardiac Disorders

Exercise intolerance is a hallmark symptom of many childhood cardiac diseases, including congestive heart failure and cyanotic congenital heart disease. Tetralogy of Fallot is discussed here because it is the most common form of cyanotic congenital heart disease and provides an interesting example of how disruption of the Fick components can differ in the preoperative versus postoperative child.

TETRALOGY OF FALLOT

Tetralogy of Fallot is a congenital disease consisting of a ventricular septal defect, pulmonary stenosis, overriding aorta, and right ventricular hypertrophy. As shown in the Figure, disruptions in the Fick relationships tend to differ in children before and after corrective surgery. In the child who has not undergone surgery, significant exercise intolerance results from severe systemic oxygen desaturation that is caused by exercise-induced increases in the pressure gradient across the stenotic area, resulting in as much as a fourfold increase in the shunting of deoxygenated blood from the right to the left ventricle. Fortunately, most children who have tetralogy of Fallot undergo complete surgical repair prior to age 2 years, with approximately 90% of patients experiencing excellent long-term clinical results. Following surgery, children tend to be unaffected in their routine physical activities, but they often display exercise intolerance during maximal physical challenges. Several factors may contribute to this, such as significant pulmonary valve regurgitation and reduced cardiac output due to blunted increases in stroke volume and heart rate. Improved exercise tolerance has been observed in postoperative children following aerobic training programs of 6 to 12 weeks duration, with greater increases in $\dot{V}O_2$ max (~ 25% increase) observed in programs of longer duration and more vigorous training.

Muscular Disorders

Muscle weakness is a frequent cause of exercise intolerance. The etiologies of muscle weakness are numerous; some involve inherited defects, as discussed in this section, and oth-

ers relate to behavioral traits, as examined in the final section.

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy is the most common childhood muscular dystrophy, affecting approximately 1 in 3,500 boys. The progressive muscular weakness that characterizes this disease makes exercise intolerance inevitable. During the ambulatory portion of the patient's life, exercise intolerance appears to result primarily from lower-than-normal oxygen consumption at the level of the muscle fibers, which is proportional to the disease-associated loss of active muscle tissue. As the disease progresses, other aspects of the Fick equation can become compromised: Myocardial weakness reduces stroke volume and diaphragmatic wasting compromises ventilation and Ca_{O_2}. Although the extent to which physical training programs can dampen the progressive decline in exercise capacity appears to be modest, it is important to keep children physically active for the psychological benefits.

In the pediatric population, exercise intolerance is associated most frequently with dysfunctions of the pulmonary, cardiovascular, and neuromuscular systems. . . .

Hematologic Disorders

IRON DEFICIENCY ANEMIA

Iron deficiency anemia is the most common childhood anemia in the United States. The reduced hemoglobin (Hb) concentration in this disease alters normal Fick equation values by diminishing the oxygen-carrying capacity of arterial blood, with the extent of the exercise intolerance related to the severity of the anemia. Many children who have mild anemia (Hb, 10 to 12 g/dL) continue to perform well at low and moderate exercise intensities by compensating for the reduced Ca_{O_2} by increasing cardiac output. In moderate (Hb, 7 to 10 g/dL) and severe (Hb, <7 g/dL) anemia or during maximal exercise in mild anemia, increased cardiac output cannot compensate for the blood's decreased oxygen content, and exercise capacity is reduced.

Treating the underlying anemia is the first step in addressing the exercise intolerance. Current (1998) Centers for Disease Control and Prevention guidelines recommend treating iron deficiency anemia in school-age children with one 60-mg iron tablet per day and adolescent boys with two 60-mg iron tablets per day (along with appropriate follow-up). Adolescent girls who have iron deficiency anemia require an oral dose of 60 to 120 mg of iron per day and appropriate follow-up. In adult studies, increases in Hb concentrations following iron supplementation have been associated with increased $\dot{V}O_2$ max. Similar studies in children are lacking.

SICKLE CELL ANEMIA

Sickle cell disease includes a group of hemoglobin disorders, the most common of which is sickle cell anemia (SCA), which has a prevalence of 1 in 375 African-American live births. The primary reason for exercise intolerance in those who have SCA is their low Hb levels, which alters the Fick equation through reduced Ca_{O_2}. Other exercise-limiting conditions associated with SCA include pulmonary disorders, cardiovascular dysfunction, and chronic inflammation. In addition, the risk of painful vaso-occlusive crises may be increased by some of the physiologic changes that occur with strenuous exercise, such as metabolic acidosis, hypoxemia, and inflammation. For these reasons, people who have SCA are not encouraged to exercise strenuously. However, it is possible that some of the exercise intolerance exhibited by these patients is the result of excessive exercise restriction. Low-to-moderate levels of exercise have been found to be beneficial in patients who have a variety of other serious diseases, including end-stage renal disease, cancer, and acquired immunodeficiency syndrome. Consequently, it may be reasonable to encourage children who have SCA to exercise at low-to-moderate levels to improve their exercise tolerance and obtain the psychological benefits of exercise and the improved working capacity.

Psychogenic and Behavioral Causes

Exercise intolerance may reflect etiologies other than overt disease states. Psychogenic and behavioral causes of exercise intolerance can affect large numbers of children and may present treatment scenarios that are poorly defined.

VOCAL CORD DYSFUNCTION

Vocal cord dysfunction describes a psychogenic disorder defined by paradoxic adduction of the vocal cords during inspiration. In the pediatric population it is seen most often among adolescent girls. Vocal cord dysfunction can mimic EIA and, in adolescents who are unresponsive to established treatments for EIA, should be considered as a possible diagnosis. Symptoms include inspiratory wheezing, throat tightness, and dyspnea during exercise. Distracting the sufferer usually results in relief of symptoms. As with EIA, vocal cord dysfunction limits exercise performance via airway obstruction, thereby reducing the Ca_{O_2} component of the Fick equation. A definitive diagnosis is established by direct observation of the vocal cords of a patient who is experiencing symptoms, using flexible fiberoptic rhinolaryngoscopy. In asymptomatic patients, an exercise challenge can be employed to induce symptoms. Speech therapy that is designed to help patients relax the laryngeal muscles during inspiration has proven successful.

SEDENTARINESS

Sedentariness is associated with deconditioning, muscle weakness, and obesity and places a greater number of children at risk for exercise intolerance than any other disorder presented in this review. The Surgeon General's 1996 report on physical activity and health noted

that only about 50% of young people in the United States participate regularly in vigorous physical activity; 25% report no vigorous physical activity. These findings are due partly to the decline in school-based physical education programs and to less time spent outdoors due to concerns about children's safety.

Sedentariness can compromise at least two components of the Fick equation. Compared with their more active counterparts, sedentary individuals display a lower maximal cardiac output, due primarily to a lower maximal stroke volume. At the tissue level, oxygen use is reduced due to low numbers and volume of mitochondria and low muscle capillary density. Thus, both delivery of oxygen via the cardiac output and use of oxygen by the metabolic machinery of working muscles are suboptimal. Obtaining an accurate patient history is especially important when sedentariness is suspected as the cause of exercise tolerance. Parental responses to queries regarding the amount of time spent by the child in sedentary activities such as watching TV and playing video games can be revealing, as are the subjective impressions of the parents regarding the physical activity level of their child compared with that of other children.

One means of treating childhood sedentariness involves integrating behavioral modification within the context of a parental or family-based intervention. A promising strategy has parents combining positive reinforcement of children for increasing their physical activity with positive reinforcement (eg, a trip to the park) for decreasing sedentary activities. This approach appears to be more effective than restricting access to sedentary activities (eg, no TV watching after school). At the community level, support is needed for increased physical education in the schools and more supervised and safe community recreational opportunities for children. Although the optimal dose of physical activity for treating the exercise-intolerant child is not well-defined, the recent (1996) National Institutes of Health consensus statement that children obtain at least 30 minutes of moderate intensity physical activity per day probably underestimates the dose needed by children who are exercise intolerant. In fact, the current (1998) recommendation by the National Association for Sport and Physical Education that school-age children accumulate at least 30 to 60 minutes of daily physical activity appears more appropriate. In many cases, sedentariness and exercise intolerance are accompanied by obesity. Recommendations from a 1998 expert committee on obesity evaluation and treatment included: 1) intervening early in life (ie, when children ≥3 years of age become overweight), 2) involving all family members and caregivers in assisting children increase their physical activity levels, and 3) emphasizing behavior changes associated with physical activity rather than weight changes.

To reiterate, during routine office visits of children who have reached the ambulatory stage, pediatricians may find it helpful to query parents about the physical activity patterns and responses of their children. Early rather than later identification of exercise intolerance could translate into more favorable outcomes for this population.

SUGGESTED READING

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PIR QUIZ

Quiz also available online at www.pedsinreview.org.

Exercise tolerance is correlated with oxygen consumption; that is, the more oxygen that is available and consumed, the better a person's exercise tolerance. The Fick formula is used to determine maximal oxygen consumption, and, therefore, the upper limit of a person's exercise tolerance. Conditions that adversely affect any of the elements of the equation will reduce the maximal level of oxygen consumption available to the patient, thereby reducing exercise tolerance. In the following, match the effect on oxygen consumption with the condition.

1. Blunted increases in heart rate
2. Increased oxygen level of mixed venous blood
3. Reduced oxygen level of arterial blood
4. Behavioral modification as part of a family-based intervention may be appropriate for which of the following causes of exercise tolerance:
   A. Cystic fibrosis.
   B. Sedentariness.
   C. Sickle cell anemia.
   D. Vocal cord dysfunction.

Exercise Intolerance

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patients infected with *H influenzae* type b. When other agents are involved, positive cultures occur in 60% to 80% of cases. Joint fluid that exhibits the characteristics of pyogenic infection may not yield bacterial pathogens in up to 30% of patients who never have received antibiotics because synovial fluid exerts a bacteriostatic effect. However, if the fluid white blood cell count is higher than 20 x 10^9/L (20 x 10^3/mcL) and there are more than 75% neutrophils, suspicion of septic joint arthritis should be high. Diagnosis and therapy are optimized if that suspicion leads to obtaining blood and joint fluid cultures before antibiotics are started for other reasons.

It was believed early in her course that this child might have toxic synovitis of the hip. Toxic synovitis is a common condition in younger children in whom the pain is accompanied by normal or slightly elevated temperature, the symptoms are mild, and there is minimal guarding on manipulation of the joint. The white blood cell count and ESR are normal or slightly elevated. Septic arthritis usually is characterized by higher temperature, more pronounced spasm and guarding on examination, and significant increases in the ESR as well as a leukocytosis with increased neutrophils and band forms. Radiographs may be normal in both conditions. A bone scan obtained early in the disease course is likely to show increased uptake in both septic arthritis and toxic synovitis because of increased vascular flow and, thus, may not be helpful. Images obtained later in the course of a clinical condition are diagnostic for processes that involve the bone (tumor, trauma, or infection).

MANAGEMENT

Therapy of septic arthritis is based on the findings from a Gram stain of joint fluid and on the knowledge of which bacteria are likely to produce disease at a particular age. Intravenous administration of methicillin, oxacillin, or nafcillin is the treatment of choice for *S aureus* infections. *H influenzae* infections are treated with a second- or third-generation cephalosporin. The minimum duration of therapy for septic arthritis is 14 to 21 days; infections of the hip should be treated for at least 4 weeks. Conversion to oral therapy is appropriate when sensitivities are known and symptoms improve substantially. However, therapy must be monitored carefully to ensure compliance with medication.

LESSONS FOR THE CLINICIAN

Septic arthritis is a serious infection. If it is not diagnosed in time or if therapy is not maintained adequately, the joint and surrounding cartilage can suffer permanent damage. This case makes several important points. Disease in the hip can manifest as pain in the thigh or knee. Radiographic findings are likely to be normal early in the course of septic arthritis, making it necessary to consider MRI or joint aspiration when a septic process seems likely. It must be stressed that once a synovial fluid aspirate of the hip joint shows pus, the hip must be explored immediately. Although this patient had impetigo, it is difficult to prove that the skin infection was the source of the joint infection; most patients who have staphylococcal skeletal infections do not have pyoderma. Nonetheless, when considering the diagnosis of septic arthritis, look for a focus of infection.

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DEPARTMENT OF CORRECTIONS

Erratum

The PIR Quiz that accompanies the Exercise Intolerance article in the January 2000 issue (page 9) does not include the answer options for questions 1, 2, and 3. This matching question should read:

1. Blunted increases in heart rate
2. Increased oxygen level of mixed venous blood
3. Reduced oxygen level of arterial blood
   A. Anemia.
   B. Congestive heart failure.
   C. Muscular dystrophy.
   D. Tetralogy of Fallot (postoperative).

Readers should match the effect on oxygen consumption with the condition.

We apologize for any confusion that this inadvertent omission caused.

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